REMARKS

Reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.116, and in light of the remarks which follow, are respectfully requested.

At the outset, it is respectfully noted that the claims are amended substantially as in the previous §116 reply, except that a wherein clause has been inserted in Claim 1 as suggested by the Examiner. The Examiner advised in a telephonic interview, that this amendment would be entered and that it would overcome the outstanding §112 issues. Therefore, upon entry of the amendment, the only potential issues that should remain are the prior art issues.

Applicants respectfully maintain that the claimed invention is non-obvious over the prior art for the reasons set forth in Applicants' previous reply submitted on January 15, 1998. Essentially, for the reasons set forth in that Reply, the prior art does not fairly teach or suggest the use of peptides containing the subject lysine-proline-valine tripeptide sequence, wherein the proline moiety of such peptide exists in its dextrorotatory optical isomer form. Essentially, the prior art alone or in combination fails to teach or suggest the anti-inflammatory activity of the subject peptides. Moreover, the prior art, in fact teaches against the subject invention.

Based on Applicants' review of the Advisory Action, it would appear that this argument was perhaps not emphasized sufficiently in Applicants' previous Reply. In particular, it is noted that in the Advisory Action, the Examiner indicates that the argument with respect to *Oluyomi et al*, was not found persuasive, because this reference assertedly suggest the use of peptides as claimed for treating inflammatory pain. Moreover, the Examiner asserts that the Hiltz reference "clearly shows that they the (sic) peptides do have the [inflammatory] effect". In support thereof, the Examiner refers to the discussion of the test models used, one a formalin test, which assertedly are similar to the administration of carrageenin which causes inflammatory hyperalgesia i.e., inflammatory pain. However, this conclusion can not be sustained. Upon careful review of the *Hiltz et al* reference, it can be clearly seen that the authors concluded based on their results, that peptides which comprised the subject tripeptide sequence, which comprises a dextrorotatory proline, were inactive, i.e., exhibited no anti-inflammatory activity. This is readily apparent based on the results of the ear swelling test, cited in the abstract of the reference, wherein they disclose that AC-[D-Pro^{12}]α-MSH(11-13)-NH_2 was inactive. By contrast, the authors report that peptides comprising other dextrorotatory amino acids, in particular a dextrorotatory form of valine, exhibited greater anti-inflammatory activity than the apparent tripeptide molecule. Moreover, the authors concluded based on their results that the "L-Pro^{12} is essential for the anti-inflammatory

activity of" the peptides disclosed in the reference. Therefore, Applicants respectfully maintain that the only reasonable conclusion that can be drawn from the *Hiltz et al* reference is that the authors concluded that the presence of the levorotatory form of proline is essential for the activity of peptides comprising the lysine-proline-valine tripeptide sequence. Indeed, the peptides used in the subject invention do not comprise this residue. By contrast, the peptides used in the claimed methods comprise the dextrorotatory form of proline, i.e., D(Pro).

Moreover, contrary to the statement made in the Office Action, Applicants respectfully note that the statements made in the abstract do not relate to a summary of the prior art. By contrast, *Hiltz et al* conclude based on their results, i.e., the data in the reference, that peptides which do not contain the L-Pro amino acid do not possess anti-inflammatory activity. Moreover, Applicants have further carefully reviewed the results disclosed in the reference. These results support the authors' conclusion, i.e., their belief (erroneous) that peptides containing the recited tripeptide, which contains the dextrorotatory form of proline, do not possess anti-inflammatory activity.

Also, Applicants respectfully maintain that these arguments are not contravened by the *Oluyomi et al* reference. Upon careful review thereof, it may be clearly seen that when the authors refer to inflammatory peptides, that they are relying on the results of *Hiltz* and *Lipton* 1989 and 1991. As discussed, these results relate to tripeptides which

comprise the levorotatory form of proline. Therefore, *Oluyomi et al* also fails to teach or suggest that the subject tripeptide, which comprises the dextrorotatory form of proline, would exhibit anti-inflammatory activity. As previously argued, *Oluyomi et al* merely suggests the anti-nociceptive activity of the subject peptides. Thus, the reference indicates that such peptides have utility for the control of pain. However, pain is attributable to many causes. Therefore, it could not be reasonably extrapolated based on the teachings of the reference, that such peptides could be used for the treatment of inflammation. Such a conclusion especially could not be made, based on the express negative teaching in *Hiltz et al*. As discussed above, and as expressly stated in the reference, the authors concluded based on their results, that peptides comprising the subject tripeptide do not possess anti-inflammatory activity. Therefore, Applicants respectfully maintain that the prior art actually teaches against the claimed invention.

Moreover, the indication that some compounds capable for treating pain also exhibit anti-inflammatory effects also does not substantiate the rejection. As previously argued, many compounds which affect (treat) pain do not exhibit anti-inflammatory activity. Moreover, the express teachings of *Hiltz*, cited in *Oluyomi et al* would teach against the invention, since the reasonable expectation would have been that peptides comprising the recited tripeptide sequence would not possess anti-inflammatory activity. Therefore, based on the foregoing, withdrawal of the prior art rejections, and allowance

of this application is respectfully believed to be in order. If the Examiner has any questions concerning this application afer review of this Response, she is respectfully requested to contact the undersigned.

Respectfully submitted,

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